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SCANNING THE LITERATURE

Summaries of Key Journal Articles

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Arrhythmias

Maintenance of Sinus Rhythm With an Ablation Strategy in Patients With Atrial Fibrillation Is Associated With a Lower Risk of Stroke and Death

Hunter RJ, McCready J, Diab I, et al.
***Circ Arrhythm Electrophysiol* 2011;Dec 7:[Epub ahead of print].**

Study Question: Does catheter ablation (CA) of atrial fibrillation (AF) improve long-term outcomes?

Methods: CA of AF (paroxysmal in 56%) was performed in 1,273 patients (mean age 58 years) enrolled in an ablation registry. Success was defined as freedom from AF/tachycardia after a 3-month blanking period. The rates of stroke and death were compared between patients with and without recurrent AF, and patients who underwent CA and a cohort with medically-treated AF. Outcomes also were compared with a hypothetical age/gender-matched group in the general population, based on United Kingdom national statistics.

Results: The procedural major complication rate was 5.4%. The mean duration of follow-up after a mean of 1.8 procedures was 2.2 years. Freedom from AF was achieved in 85% of patients with paroxysmal AF and 72% with persistent AF. Freedom from AF was independently associated with a 70% reduction in stroke/mortality. The annual stroke/mortality rates (0.5% for each) were significantly lower in the CA patients than in the medically-treated cohort (2.8% and 5.3%, respectively), and similar to the stroke/mortality rates in the general population (0.4% and 1.0%, respectively).

Conclusions: Successful CA of AF lowers the risk of stroke and death.

Perspective: The AFFIRM study showed that maintenance of sinus rhythm was independently associated with reduced mortality, but that this effect was neutralized by the deleterious effects of antiarrhythmic drug therapy. Given the limitations of registry data and historical controls, the conclusions of this study are tentative, but the results suggest that maintenance of sinus rhythm without need for antiarrhythmic drug therapy can improve outcomes.

Summary written by: Fred Morady, MD

Subclinical Atrial Fibrillation and the Risk of Stroke

Healey JS, Connolly SJ, Gold MR, at al.
***N Engl J Med* 2012;366:120-129.**

Study Question: Do asymptomatic episodes of atrial tachyarrhythmia (AT) detected by a pacemaker or implanted cardioverter-defibrillator (ICD) increase the risk of stroke?

Methods: The subjects were 2,580 patients who underwent implantation of a pacemaker or ICD. The selection criteria were age ≥65 years (mean age 76 years), hypertension, and no history of atrial fibrillation (AF). A subclinical AT was defined as an asymptomatic atrial high-rate event >190 bpm lasting >6 minutes. Patients in whom ATs were noted at 3 months of follow-up were randomly assigned to receive or not receive continuous atrial overdrive pacing. The primary outcome was ischemic stroke or systemic embolism.

Results: Subclinical ATs (median two/patient, mean rate 480 bpm) were noted in 10.1% of patients at 3 months of fol-

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low-up. During the entire follow-up, subclinical ATs were noted in 34.6% of patients and clinical AF occurred in 15.7% of patients. During a mean of 2.5 years of follow-up, the annual risk of stroke/embolism was significantly higher in patients with than without a subclinical AT detected at 3 months (1.7% vs. 0.7%, hazard ratio [HR], 2.5). During follow-up, AT episodes >6 minutes, >6 hours, and >24 hours were associated with a similar degree of increased risk of stroke/embolism (HRs 1.8, 2.0, and 2.0, respectively). Continuous atrial overdrive pacing did not prevent ATs.

Conclusions: Asymptomatic AF detected by cardiac devices is associated with an increased risk of stroke/embolism.

Perspective: Because only AT episodes longer than 6 minutes were included in the analysis, the minimum duration of subclinical ATs associated with thromboembolic complications is unclear. Whether anticoagulation has a net benefit in patients with subclinical ATs also remains to be determined.

Summary written by: Fred Morady, MD

Cardiac Arrest During Long-Distance Running Races

Kim JH, Malhotra R, Chiampas G, et al., on behalf of the Race Associated Cardiac Arrest Event Registry (RACER) Study Group
***N Engl J Med* 2012;366:130-140.**

Study Question: What are the incidence and outcomes of cardiac arrest associated with marathon and half-marathon races in the United States?

Methods: The incidence and outcomes of cardiac arrest associated with marathon and half-marathon races in the United States were assessed from January 1, 2000, to May 31, 2010. The clinical characteristics of the arrests were determined by interviewing survivors and next of kin of nonsurvivors, reviewing medical records, and analyzing postmortem data.

Results: Of 10.9 million runners, 59 (mean [± standard deviation] age 42 ± 13 years; 51 men) had cardiac arrest (incidence rate 0.54 per 100,000 participants). Cardiovascular disease accounted for the majority of cardiac arrests. The incidence rate was significantly higher during marathons (1.01 per 100,000) than during half-marathons (0.27), and among men (0.90 per 100,000) than among women (0.16). Male marathon runners, the highest-risk group, had an increased incidence of cardiac arrest during the latter half of the study decade (2000-2004, 0.71 per 100,000; 2005-2010, 2.03 per 100,000; p = 0.01). Of the 59 cases of cardiac arrest, 42 were fatal (incidence, 0.39 per 100,000). Among the 31 cases with complete clinical data, initiation of bystander-administered cardiopulmonary resuscitation and an underlying diagnosis other than hypertrophic cardiomyopathy were the strongest predictors of survival.

Conclusions: Marathons and half-marathons are associated with a low overall risk of cardiac arrest and sudden death. Cardiac arrest, most commonly attributable to hypertrophic cardiomyopathy or atherosclerotic coronary disease, occurs primarily among male marathon participants; the incidence rate in this group increased during the past decade.

Perspective: I run marathons. If I die during a marathon, I am OK with it. This study does an excellent job in demonstrating that cardiovascular death occurs during distance races, but that it is rare. Exercise has dramatic physical and mental benefits. Even if it does not confer immortality, physicians should emphasize the benefits of exercise rather than perseverating on the rare cardiac death that happens to occur during an athletic event.

Summary written by: David S. Bach, MD

Cardiovascular Surgery

Bridging Antiplatelet Therapy With Cangrelor in Patients Undergoing Cardiac Surgery: A Randomized Controlled Trial

Angiolillo DJ, Firstenberg MS, Price MJ, et al., on behalf of the BRIDGE Investigators.
***JAMA* 2012;307:265-274.**

Study Question: What is the effect of cangrelor, an intravenous, reversible $P2Y_{12}$ platelet inhibitor, for bridging thienopyridine-treated patients to coronary artery bypass grafting (CABG) surgery?

Methods: BRIDGE was a prospective, randomized, double-blind, placebo-controlled, multicenter trial, involving 210 patients with an acute coronary syndrome or treated with a coronary stent and receiving a thienopyridine awaiting CABG surgery to receive either cangrelor or placebo after an initial open-label, dose-finding phase (n = 11) conducted between January 2009 and April 2011. Thienopyridines were stopped and patients were administered cangrelor or placebo for at least 48 hours, which was discontinued 1-6 hours before CABG surgery. The primary efficacy endpoint was platelet reactivity (measured in $P2Y_{12}$ reaction units [PRUs]), assessed daily. The main safety endpoint was excessive CABG surgery–related bleeding. The primary efficacy endpoint, the percentage of patients who maintained a PRU <240 during study drug infusion prior to surgery, was analyzed.

Results: The dose of cangrelor determined in 10 patients in the open-label stage was 0.75 μg/kg per minute. In the randomized phase, a greater proportion of patients treated with cangrelor had low levels of platelet reactivity through the entire treatment compared with placebo (primary endpoint, PRU <240; 98.8% vs. 19.0%; relative risk [RR], 5.2; p < 0.001). Excessive CABG surgery–related bleeding occurred

in 11.8% versus 10.4% in the cangrelor and placebo groups, respectively (RR, 1.1; p = 0.763). There were no significant differences in major bleeding prior to CABG surgery, although minor bleeding episodes were numerically higher with cangrelor.

Conclusions: Among patients who discontinue thienopyridine therapy prior to cardiac surgery, the use of cangrelor compared with placebo resulted in a higher rate of maintenance of platelet inhibition.

Perspective: This study suggests that cangrelor infusion consistently achieved and maintained platelet inhibition at levels known to be associated with a low risk of thrombotic events compared with placebo. Furthermore, bridging with a prolonged infusion of cangrelor did not increase major bleeding prior to surgery, although minor bleeding was higher. Thus, intravenous cangrelor appears to be a feasible management strategy in patients waiting for cardiac surgery who require prolonged platelet $P2Y_{12}$ inhibition after thienopyridine discontinuation.

Summary written by: Debabrata Mukherjee, MD

Mild-to-Moderate Functional Tricuspid Regurgitation in Patients Undergoing Valve Replacement for Rheumatic Mitral Disease: The Influence of Tricuspid Valve Repair on Clinical and Echocardiographic Outcomes

Kim JB, Yoo DG, Kim GS, et al.
***Heart* 2012;98:24-30.**

Study Question: Should concomitant tricuspid valve repair be performed among patients with mild-to-moderate functional tricuspid regurgitation (TR) undergoing mitral valve surgery?

Methods: Between 1997 and 2009, 236 patients with mild-to-moderate functional TR underwent first-time isolated mechanical MVR for rheumatic mitral disease. Of these, 123 underwent concomitant tricuspid valve repair (repair group) and 113 did not (nonrepair group). Survival, valve-related complications, and tricuspid valve function in the two groups were compared after adjustment for baseline characteristics using inverse-probability-of-treatment weighting.

Results: Follow-up was complete in 225 patients (95.3%), with a median follow-up of 48.7 months. During that time, 991 echocardiographic assessments were done. Freedom from moderate-to-severe TR at 5 years was 92.9 ± 2.9% in the repair group and 60.8 ± 6.9% in the nonrepair group (p < 0.001 and 0.048 in crude and adjusted analyses, respectively). After adjustment, both groups had similar risks of death (hazard ratio [HR], 0.57; p = 0.43), tricuspid reoperation (HR, 0.10; p = 0.080), and congestive heart failure (HR, 1.12; p = 0.87). Postoperative moderate-to-severe TR was an independent predictor of poorer event-free survival (HR, 2.90; p = 0.038).

Conclusions: The findings support a strategy of correcting mild-to-moderate functional TR at the time of MVR to maintain tricuspid valve function and improve clinical outcomes.

Perspective: This study does a nice job of showing that patients who underwent mechanical MVR had less TR on follow-up if concomitant tricuspid annuloplasty was performed. However, measured clinical endpoints did not appear to differ between groups, and it remains an act of faith that tricuspid annuloplasty results in less postoperative right-sided heart failure after otherwise successful MV surgery.

Summary written by: David S. Bach, MD

Clinical Outcomes in Non-Surgically Managed Patients With Very Severe Versus Severe Aortic Stenosis

Kitai T, Honda S, Okada Y, et al.
***Heart* 2011;97:2029-2032.**

Study Question: What are the clinical outcomes of patients with severe versus very severe aortic stenosis (AS)?

Methods. In a single-center, retrospective cohort study, 108 conservatively treated patients with severe AS (maximal jet velocity ≥4.0 m/s, mean aortic pressure gradient [MPG] ≥40 mm Hg, or aortic valve area [AVA] <1.0 cm^2) and 58 patients with very severe AS (maximal jet velocity ≥5.0 m/s, MPG ≥50 mm Hg, or AVA <0.6 cm^2) were compared. Clinical outcomes (all-cause mortality and valve-related events [defined by a composite of cardiac death and hospitalization because of heart failure]) were assessed.

Results. Mean follow-up was 5.5 ± 3.1 years. A total of 56 patients (52%) with severe AS and 20 patients (34%) with very severe AS were asymptomatic. At 3 years, very severe AS patients had poorer survival and valve-related event-free survival than did severe AS patients (77% vs. 88%, p < 0.01; 75% vs. 88%, p < 0.001, respectively). The 3-year survival and valve-related event-free survival of asymptomatic very severe AS were comparable with symptomatic severe AS, but were significantly worse than asymptomatic severe AS patients (p < 0.01 and p < 0.001, respectively).

Conclusions. Surgery should always be considered in patients with very severe AS regardless of symptoms, and particular attention needs to be paid to their extremely poor outcomes.

Perspective. The dogma that all patients with severe AS are at low risk as long as they remain asymptomatic needs to be reassessed. This study does a nice job of demonstrating that

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not all 'severe' AS is the same. Patients with very severe AS were at high risk for morbid and mortal valve-related events. In patients with severe AS, lack of symptoms should not be taken as an over-riding reason to discount consideration for surgical intervention.

Summary written by: David S. Bach, MD

Heart Valve Prosthesis Selection in Patients With End-Stage Renal Disease Requiring Dialysis: A Systematic Review and Meta-Analysis

Chan V, Chen L, Mesana L, Mesana TG, Ruel M.
***Heart* 2011;97:2033-2037.**

Study Question: Are there clinical data to support the use of a bioprosthesis versus a mechanical prosthesis among patients with end-stage renal disease (ESRD) on hemodialysis who undergo heart valve replacement?

Methods: A meta-analysis was performed using studies published in English beginning in 1990 if they compared bioprostheses with mechanical prostheses in patients with ESRD on dialysis. Extracted summary estimates included the hazard ratio (HR) for death and odds ratio (OR) for developing valve-related complications due to use of bioprostheses versus mechanical prostheses.

Results: Twelve studies published from 1997 to 2010 were included in this review, of which nine were used in the meta-analysis. In these studies, the aortic valve was the most common valve replaced (4,339 of 6,350), although 11 of the 12 studies also included mitral or multiple valve replacements. No difference in survival was observed between valve types (bioprosthesis vs. mechanical prosthesis, HR, 1.3; p = 0.09). However, valve replacement with a bioprosthesis was associated with fewer valve-related complications compared to a mechanical prosthesis (OR, 0.4; p = 0.002).

Conclusions: A meta-analysis of the published literature demonstrated no survival difference following valve replacement with either a bioprosthesis or mechanical prosthesis in patients with ESRD on dialysis. Bioprosthetic valve replacement was associated with fewer valve-related complications. The authors concluded that the data can likely be extended to include at least aortic valve replacement.

Perspective: This meta-analysis confirms that fears of higher mortality after bioprosthetic valve replacement are unfounded. Avoiding long-term Coumadin therapy among patients who typically require three-times weekly vascular access for hemodialysis likely contributes to fewer valve-related complications in association with a bioprosthesis.

Summary written by: David S. Bach, MD

General

CYP2C19 Genotype, Clopidogrel Metabolism, Platelet Function, and Cardiovascular Events: A Systematic Review and Meta-Analysis

Holmes MV, Perel P, Shah T, Hingorani AD, Casas JP.
***JAMA* 2011;306:2704-2714.**

Study Question: What is the evidence on the association of *CYP2C19* genotype and clopidogrel response?

Methods: Studies that reported clopidogrel metabolism, platelet reactivity, or clinically relevant outcomes (cardiovascular disease [CVD] events and bleeding), and information on *CYP2C19* genotype were included. The investigators extracted information on study design, genotyping, and disease outcomes, and investigated sources of bias. They estimated absolute risk differences between genotype categories based on the control group event rate from the CURE (acute coronary syndrome) and CHARISMA (stable coronary heart disease) trials and the trim-and-fill summary relative risk (RR) (to minimize small-study bias), comparing carriers of any loss-of-function *CYP2C19* allele versus the reference category, and assuming consistency of RRs across a range of baseline absolute risks of cardiovascular and bleeding events.

Results: The authors retrieved 32 studies of 42,016 patients reporting 3,545 CVD events, 579 stent thromboses, and 1,413 bleeding events. Six studies were randomized trials ("effect-modification" design) and the remaining 26 reported individuals exposed to clopidogrel ("treatment-only" design). In treatment-only analysis, individuals with one or more *CYP2C19* alleles associated with lower enzyme activity had lower levels of active clopidogrel metabolites, less platelet inhibition, lower risk of bleeding (RR, 0.84; absolute risk reduction of 5-8 events per 1,000 individuals), and higher risk of CVD events (RR, 1.18; absolute risk increase of 8-12 events per 1,000 individuals). However, there was evidence of small-study bias. When analyses were restricted to studies with 200 or more events, the point estimate was attenuated (RR, 0.97). In effect-modification studies, *CYP2C19* genotype was not associated with modification of the effect of clopidogrel on CVD endpoints or bleeding (p > 0.05 for interaction for both).

Conclusions: Although there was an association between the *CYP2C19* genotype and clopidogrel responsiveness, overall there was no significant association of genotype with CV events.

Perspective: This systematic review and meta-analysis does not demonstrate a clinically important association of *CYP2C19* genotype with CV outcomes with the possible exception of stent thrombosis. A large randomized controlled trial is needed to adequately test the clopidogrel pharma-

cogenomic hypothesis and its clinical significance. Pending such a study, physicians should use *CYP2C19* or platelet reactivity testing rarely, if ever, and interpret the results with appropriate caution.

Summary written by: Debabrata Mukherjee, MD

Serum Potassium Levels and Mortality in Acute Myocardial Infarction

Goyal A, Spertus JA, Gosch K, et al.
***JAMA* 2012;307:157-164.**

Study Question: What is the association between average serum potassium during hospitalization and the outcome of patients with acute myocardial infarction (AMI)?

Methods: The authors retrospectively evaluated the outcome of 38,689 patients in the Cerner Health Facts database, who were hospitalized with biomarker-confirmed AMI, to 67 US hospitals from 2000-2008. All patients had in-hospital serum potassium measurements and were categorized by mean postadmission serum potassium level. Hierarchical logistic regression was used to determine the association between potassium levels and outcomes after adjusting for patient- and hospital-level factors.

Results: A U-shaped relationship between mean postadmission serum potassium level and in-hospital mortality persisted after multivariable adjustment for multiple factors. The mortality among the reference group with potassium (K) levels of 3.5-<4.0 mEq/L was 4.8%, and was similar in those with postadmission potassium of 4.0-<4.5 mEq/L (5.0%). Mortality increased with an increase in serum potassium (K 4.5-<5.0 mEq/L, mortality 10.0%; K 5-<5.5 mEq/L, mortality 24.8%; K >5.5 mEq/L, mortality 61.4%). A lesser degree of increase in mortality was observed with decreasing average potassium levels (K <3 mEq/L, mortality 46.2%; K 3-<3.5 mEq/L, mortality 11.4). Rates of ventricular fibrillation or cardiac arrest were higher only among patients with potassium levels of <3.0 mEq/L and at levels of 5.0 mEq/L or greater.

Conclusions: Among patients hospitalized with AMI, the lowest mortality was observed in those with postadmission serum potassium levels between 3.5 and <4.5 mEq/L compared with those who had higher or lower potassium levels.

Perspective: There was a disconnect between occurrence of cardiac arrest or ventricular fibrillation and total mortality at both extremes in this study; an increase was seen only with extreme levels of serum potassium. This raises concern about residual confounding and reverse causality, the elegant analytical design notwithstanding. Although prior guidelines are based on a small body of observational data, it may be premature to change current practice without randomized data.

Summary written by: Hitinder S. Gurm, MBBS

International Variation in and Factors Associated With Hospital Readmission After Myocardial Infarction

Kociol RD, Lopes RD, Clare R, et al.
***JAMA* 2012;307:66-74.**

Study Question: What is the international variation in readmission rates among patients treated with primary percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (STEMI)?

Methods: The authors retrospectively evaluated the country level variation in readmission among 5,745 patients with STEMI enrolled in the Assessment of Pexelizumab in Acute Myocardial Infarction trial. This trial enrolled 5,745 patients with STEMI at 296 sites in the United States, Canada, Australia, New Zealand, and 13 European countries. Multivariable logistic regression analysis was used to identify independent predictors of all-cause and nonelective 30-day post-discharge readmission.

Results: Of the 5,571 patients discharged alive, 11.3% were readmitted within 30 days. US patients had higher 30-day readmission rates (14.5% vs. 9.9%). Median length of stay was shortest for US patients (3 days) and longest in patients from Germany (8 days). The predictors of all-cause 30-day readmission included multivessel disease (odds ratio [OR], 1.97) and US location (OR, 1.68), but multivessel disease was not significant when admission for elective revascularization was excluded. Enrollment in the US was, however, an independent predictor of readmission (OR, 1.53) after excluding elective readmissions for revascularization. After adjustment for country-level median length of stay, US location was no longer an independent predictor of 30-day all-cause or nonelective readmission. There was an inverse relation between country-level median length of stay and readmission, with a 14% reduction in the odds of readmission for each additional in-hospital day (OR, 0.86). There was no impact of US enrollment on in-hospital death (OR, 0.88) or 30-day post-admission death (OR, 1.0).

Conclusions: There was significant variation in the rate of readmission among patients with STEMI, with the US having the highest rates of readmission.

Perspective: There is increasing interest in readmission after hospitalization after STEMI as a quality and an economic measure. This study demonstrates a marked variation in readmission rates across the participating countries without differences in mortality. The higher rate of readmission in the US is counterbalanced by short length of stay, and efforts to reduce readmission may come at the cost of prolonging hospitalization. Further studies are warranted to define patient-level predictors of readmission so that focused interventions can be targeted to reduce readmission rates.

Summary written by: Hitinder S. Gurm, MBB

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Cardiovascular Mortality in Women With Obstructive Sleep Apnea With or Without Continuous Positive Airway Pressure Treatment: A Cohort Study

Campos-Rodriguez F, Martinez-Garcia MA, de la Cruz-Moron I, Almeida-Gonzalez C, Catalan-Serra P, Montserrat JM.
***Ann Intern Med* 2012;156:115-122.**

Study Question: Is obstructive sleep apnea (OSA) a risk factor for cardiovascular death in women, and does continuous positive airway pressure (CPAP) treatment reduce mortality risk?

Methods: This was a prospective observational cohort study, which enrolled women from two sleep clinics in Spain. All women were referred for suspected OSA between 1998 and 2007, and received a diagnostic sleep study. Women with an apnea–hypopnea index (AHI) less than 10 were the control group. OSA was diagnosed when the AHI was 10 or higher (classified as mild to moderate [AHI of 10-29] or severe [AHI ≥30]). Women were classified as treated if they wore their CPAP ≥4 hours per day, and untreated if CPAP was worn <4 hours per day (or not prescribed). Participants were followed until December 2009. The primary outcome was cardiovascular mortality.

Results: A total of 1,116 women were included (median follow-up, 72 months). The control group had a lower cardiovascular mortality rate (0.28 per 100 person-years) than the untreated groups with mild to moderate OSA (0.94 per 100 person-years) or severe OSA (3.71 per 100 person-years). Compared with the control group, the fully adjusted hazard ratios for cardiovascular mortality were 3.50 for the untreated, severe OSA group; 0.55 for the CPAP-treated, severe OSA group; 1.60 for the untreated, mild to moderate OSA group; and 0.19 for the CPAP-treated, mild to moderate OSA group.

Conclusions: Severe OSA is associated with increased risk of cardiovascular death in women, and adequate CPAP treatment may reduce this risk.

Perspective: OSA is associated with both cardiovascular risk factors and cardiovascular disease mortality in men. This study suggests the risk of cardiovascular disease mortality associated with OSA is also present in women. A randomized controlled trial examining treatment of OSA in relation to cardiovascular disease risk among women would be recommended, based on these findings.

Summary written by: Elizabeth A. Jackson, MD

Long-Term Cardiovascular Mortality After Procedure-Related or Spontaneous Myocardial Infarction in Patients With Non-ST-Segment Elevation Acute Coronary Syndrome: A Collaborative Analysis of Individual Patient Data From the FRISC II, ICTUS, and RITA-3 Trials (FIR)

Damman P, Wallentin L, Fox KA, et al.
***Circulation* 2011;Dec 23:[Epub ahead of print].**

Study Question: What is the long-term prognostic impact of procedure-related and spontaneous myocardial infarction (MI) on cardiovascular mortality in patients with non-ST-elevation acute coronary syndrome (NSTE-ACS)?

Methods: Five-year follow-up after procedure-related or spontaneous MI was investigated in the individual patient-pooled data set of the FRISC-II, ICTUS, and RITA-3 (FIR) NSTE-ACS trials. The principal outcome was cardiovascular death up to 5 years of follow-up. Cumulative event rates were estimated with the Kaplan-Meier method, and hazard ratios (HRs) were calculated with time-dependent Cox proportional-hazards models. Adjustments were made for variables associated with long-term outcomes.

Results: Of the 5,467 patients, 212 endured a procedure-related MI within 6 months after enrollment. A spontaneous MI occurred in 236 patients within 6 months. The cumulative cardiovascular death rate was 5.2% in patients who endured a procedure-related MI and comparable to patients without a procedure-related MI (HR, 0.66; $p = 0.17$). In patients who endured a spontaneous MI within 6 months, the cumulative cardiovascular death rate was 22.2% and higher than patients without a spontaneous MI (HR, 4.52; $p < 0.001$). These HRs did not materially alter after risk adjustments.

Conclusions: Five-year follow-up of NSTE-ACS patients from the three trials showed no association between a procedure-related MI and long-term cardiovascular mortality.

Perspective: The study findings emphasize the importance of differentiating effects on different types of MI when evaluating the efficacy and safety of new medical and interventional treatments and translating these findings for treatment recommendations. The study also raises the question of whether procedure-related MI is a valid outcome for clinical trials.

Summary written by: Debabrata Mukherjee, MD

Interventional Cardiology

Diffusion-Weighted MRI Determined Cerebral Embolic Infarction Following Transcatheter Aortic Valve Implantation: Assessment of Predictive Risk Factors and the Relationship to Subsequent Health Status

Fairbairn TA, Mather AN, Bijsterveld P, et al.
***Heart* 2012;98:18-23.**

Study Question: What are the frequency and predictors of cerebral infarction in patients undergoing transcatheter aortic valve implantation (TAVI), and its impact on patient health-related quality of life (HRQoL)?

Methods: The authors performed cerebral diffusion-weighted MRI on 31 patients before and after CoreValve TAVI. HRQoL was assessed at baseline and at 30 days by SF-12v2 and EQ5D questionnaires.

Results: New cerebral infarction on diffusion-weighted imaging was seen in 24/31 patients (77%), and stroke in 2 patients (6%). There were 131 new infarcts distributed equally between the cerebral hemispheres (left 53%, right 47%), and in multiple territories (anterior 7%, middle 59%, posterior 14%, and vertebrobasilar 20%). The average number of infarcts per patient was 4.2 and the median was 2. Stroke was associated with a greater number and volume of cerebral infarcts. Age, severity of aortic atheroma, and catheterization time were independent predictors of the number of new cerebral infarcts. HRQoL as assessed by SF-12v2 physical component summary increased significantly (32.4 vs. 36.5), with no significant change in mental component summary (43.56 vs. 43.16). The EQ5D score (0.56 vs. 0.59) and Visual Analogue Scale (54.2 vs. 58.2) showed no significant change.

Conclusions: Among patients undergoing TAVI, silent cerebral infarction is common and is associated with increased age and severity of arch atheroma.

Perspective: Stroke remains one of the most important complications of TAVI. In this small study, silent cerebral infarction was seen in most patients, and this, combined with the relatively high frequency of clinical stroke observed in other studies, invokes the need for evaluation of embolization protection devices to improve procedural safety.

Summary written by: Hitinder S. Gurm, MBB

Prevention/Vascular

Bariatric Surgery and Long-Term Cardiovascular Events

Sjöström L, Peltonen M, Jacobson P, et al.
***JAMA* 2012;307:56-65.**

Study Question: Does bariatric surgery, resulting in weight loss, reduce the risk of cardiovascular (CV) events?

Methods: Data from the Swedish Obese Subjects (SOS) study were used for this analysis. The SOS study is an ongoing nonrandomized prospective study of 2,010 obese subjects who underwent bariatric surgery and 2,037 contemporaneously matched obese controls who received usual care, recruited between September 1, 1987, and January 31, 2001. Inclusion criteria were ages 37-60 years and a body mass index (BMI) of at least 34 in men and at least 38 in women. The primary outcomes included myocardial infarction and stroke.

Results: At baseline, the mean BMI was 40.1 in the control and 42.4 in the surgery group. The mean changes in body weight after 2, 10, 15, and 20 years were −23%, −17%, −16%, and −18% in the surgery and 0%, 1%, −1%, and −1% in the control group. Surgery patients underwent gastric bypass (13.2%), banding (18.7%), or vertical banded gastroplasty (68.1%), and controls received usual care in the Swedish primary health care system. Over a median follow-up of 14.7 years, bariatric surgery was associated with a reduced number of CV deaths (28 events in the surgery vs. 49 in the control group; adjusted hazard ratio [HR], 0.47). The number of total first time (fatal or nonfatal) CV events (myocardial infarction or stroke) was lower in the surgery group (199 events in the surgery vs. 234 in the control group). Higher baseline insulin concentrations were associated with more favorable outcomes in bariatric surgery patients. No significant interactions were noted between BMI, or other metabolic and anthropometric variables, bariatric surgery, and CV outcomes.

Conclusions: Compared with usual care, bariatric surgery was associated with a reduced number of CV deaths and lower incidence of CV events in obese adults.

Perspective: This study provides evidence that bariatric surgery resulting in weight loss also lowers risk for CV outcomes, although the study is limited by the lack of randomization. Further research is need to fully understand which patients benefit the most from such surgeries, and what is key to CV risk modification.

Summary written by: Elizabeth A. Jackson, MD

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Increased Short-Term Risk of Thrombo-Embolism or Death After Interruption of Warfarin Treatment in Patients With Atrial Fibrillation

Raunso J, Selmer C, Olesen JB, et al.
***Eur Heart J* 2011;Dec 23:[Epub ahead of print].**

Study Question: What is the risk and timing of thromboembolic events associated with interruptions of warfarin treatment in atrial fibrillation?

Methods: This was a retrospective nationwide cohort study of all patients in Denmark treated with warfarin for atrial fibrillation, using the Danish National Patient Registry. Analysis included patients with nonvalvular atrial fibrillation, greater than age 30, after a first hospitalization for atrial fibrillation with subsequent use of warfarin. Warfarin use interruption was assumed to start when a patient ran out of available warfarin tablets, as calculated based on prescription claims. Incident rate ratios (IRRs) were calculated using Poisson regression for estimates of thromboembolic events and all-cause mortality.

Results: Between 1997 and 2008, 48,980 atrial fibrillation patients were identified, of which 35,396 had one estimated warfarin interruption, among whom there were 8,255 deaths or thromboembolic events associated with treatment interruption. The timing of these events was clustered as follows: 2,717, 835, 500, and 427 events occurred during 0-90, 91-180, 181-270, and 271-360 days after warfarin treatment interruption, respectively. The corresponding crude incident rates were 31.6, 17.7, 12.3, and 11.4 events per 100 patient-years. By multivariable analysis, the initial 90-day interval after treatment interruption was associated with a markedly higher risk of death or thromboembolism (IRR, 2.5; 95% confidence interval, 2.3-2.8) versus the interval between 271 and 360 days after warfarin treatment interruption.

Conclusions: In patients with atrial fibrillation, an interruption of warfarin treatment is associated with a significantly increased short-term risk of death with thromboembolic events within the first 90 days after treatment interruption.

Perspective: The study does not evaluate elective interruptions of therapy (e.g., surgical procedures), but rather identifies warfarin treatment interruption by identifying periods of time when supply of medication ran out. Furthermore, the median duration of treatment interruptions was 36 days, significantly exceeding the usual elective interruption for an invasive procedure. In spite of these limitations, the data are extremely useful, and suggest that the risk of thromboembolism or death is more than doubled within 90 days after warfarin treatment interruption for a median of 36 days.

Summary written by: James B. Froehlich, MD, MPH

Pharmacogenetic Determinants of Statin-Induced Reductions in C-Reactive Protein

Chu AY, Giulianini F, Barratt BJ, Nyberg F, Chasman DI, Ridker PM.
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Study Question: Do different mechanisms underlie statin-induced C-reactive protein (CRP) and low-density lipoprotein cholesterol (LDL-C) reduction?

Methods: This study evaluated potential genetic determinants of CRP response using genome-wide genetic data from 6,766 participants of European ancestry randomly allocated to 20 mg/day of rosuvastatin or placebo in the JUPITER trial.

Results: Among 3,386 rosuvastatin-allocated individuals, both CRP and LDL-C levels were reduced by 50% after 12 months of therapy (both p values < 0.001) and essentially uncorrelated ($r^2 < 0.03$). None of the three genes (*ABCG2, LPA*, and *APOE*) that previously showed genome-wide association with LDL-C reduction in this cohort and none of the candidate single nucleotide polymorphisms (SNPs) associated with LDL-C reduction were associated with rosuvastatin-induced CRP change after multiple testing correction. Among candidate SNPs selected from prior genetic analyses of baseline CRP, CRP reduction was associated with rs2794520 in CRP (mean -3.5% change in CRP per minor allele, $p = 6.4 \times 10^{-4}$), and with rs2847281 in *PTPN2* (mean 3.7% change in CRP per minor allele, $p = 7.4 \times 10^{-4}$). Neither variant was associated with rosuvastatin-induced LDL-C reduction or with CRP reduction among 3,380 placebo-allocated JUPITER participants.

Conclusions: The genetic determinants of rosuvastatin-induced CRP reduction differ from, and are largely independent of, the major pharmacogenetic determinants of rosuvastatin-induced LDL-C reduction. This supports the hypothesis that differing pathways may mediate the anti-inflammatory and lipid-lowering properties of statin therapy.

Perspective: There is evidence that the reduction in cardiovascular event rate in placebo-controlled primary and secondary coronary heart disease prevention trials with atorvastatin, pravastatin, and rosuvastatin is related to both magnitude of reduction in LDL-C and achieving a high-sensitivity CRP <1 mg/L. Based on this study, the degree to which different statins influence the genetic determinants of CRP and immune function may impact their clinical efficacy independent of lipid-lowering effect, a posit not accepted by many.

Summary written by: Melvyn Rubenfire, MD